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Short-lived immunity against pertussis, age-specific routes of transmission, and the utility of a teenage booster vaccine

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ABSTRACT

Background: Pertussis incidence has been increasing for the past two decades in Norway, as in much of the highly vaccinated world. The greatest increase is in teenagers, although the most severe cases occur in infants. A teenage booster is recommended globally, largely with the aim of reducing infant incidence. However few countries have implemented the booster, and almost no data have been published on its utility in preventing infant cases. We aim to assess the duration of vaccine-induced immunity, and the possibility for a teenage-booster vaccine to protect infants in Norway.
Methods and findings: We used a unique data set that merged case reports with a national vaccine registry from Norway, 1996–2010, to assess age- and cohort-specific hazards of infection. We also developed and implemented a likelihood-based method for estimating the duration of immunity, taking into account age-contact data relevant for pertussis transmission. The risk of infection in thirteen-year olds increased nearly four-fold, however the hazard in infants did not significantly change. The seasonality of cases in pre-school-aged children differed from that of school-aged children. The introduction of a childhood booster vaccine provided indirect protection for unvaccinated members of the cohort, but little protection to neighboring cohorts. Additionally, we found evidence for increasingly rapid infection after three doses of vaccine, potentially caused by significant and heterogeneous loss of immunity. An estimated 15% of vaccinated individuals lost their immunity within five years after vaccination.
Conclusions: Immunity induced by the acellular pertussis vaccine prevents both disease and transmission, but is short-lived and heterogeneous. The age-mixing patterns lead to little contact between teenagers and infants. Therefore, while a teenage booster vaccine campaign would likely provide strong protection for cohorts of teenagers, it would provide little protection for infants.
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1. Introduction

Pertussis incidence has been increasing for the past two decades in Norway, as in much of the highly vaccinated world. The greatest increase has been in teenagers, although the most severe pertussis cases occur in infants. The Global Pertussis Initiative recommends that all countries that can afford it should institute an adolescent booster vaccination campaign to reduce overall incidence and cases in prevaccine-age infants on the assumptions that (a) the vaccine provides temporary protection, (b) loss of immunity is contributing to the teenage outbreaks, and (c) lower circulation among teenagers will provide indirect protection against severe cases in infants. Some countries, including France, Austria, Canada, the U.S.A., Australia and Germany, have already done so [1]. However, little data has been published on the coverage or results of these booster campaigns. Here we (1) assess the evidence for loss of immunity to pertussis in Norway, (2) estimate the duration of vaccine-induced immunity, and (3) predict the extent to which the addition of a proposed teenage booster vaccine would provide indirect protection for and significantly reduce incidence in infants.

Three main classes of hypotheses have been put forward to explain the widely observed patterns of pertussis re-emergence in highly vaccinated countries [2]: (1) age-specific contact patterns

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combined with low primary vaccine efficacy may explain the changing age distribution [3], (2) the increase in severe cases may be caused by vaccine-driven virulence evolution [4], and (3) increased waning of immunity due to population level effects cause more cases of severe disease in teenagers [5,6]. The first two of these hypotheses do not necessitate waning of immunity, and we therefore attempt to assess whether there is evidence that immunity is lost over time after the first three doses of vaccine.

Norway is a well-suited study system for attempting to answer these questions. First, the Norwegian Institute of Public Health maintains detailed national records of both reported pertussis cases and vaccination histories. Second, they fit the global pattern of developed countries experiencing a resurgence, particularly in teenagers. Third, a childhood booster vaccine was introduced in 2006 and detailed data is available from both before and after the introduction creating a natural experiment.

Norway began vaccinating against pertussis in 1952. Throughout most of the 1980s and 1990s, vaccination was provided by a three-dose regime at ages 3, 5, and 10 months with a whole-cell vaccine produced by Wellcome Evans. In January 1998, the whole-cell vaccine was replaced by a three-component acellular vaccine, Infanrix. In 2004, reported incidence of whooping cough in Norway was the highest in Europe [7] (perhaps due in part to an increase in awareness), and so in 2006, a two-component booster acellular vaccine, Tetravac, was added at age seven years. There has been 90–97% coverage with three doses throughout the study period. The uptake of the booster vaccine at age seven was quite quick, with approximately 90% coverage by 2006.

Age-specific contact rates have been shown to be important in pertussis epidemiology with most transmission to infants coming from immediate family members, largely parents or parenting-age individuals [8,9]. A recent study on pertussis in Sweden suggested that age-specific contact rates, with high levels within age groups and between parents and children, are all that is necessary to explain the epidemiology there, with waning of immunity appearing to be a less important factor [3]. However, Sweden only recently re-introduced vaccination (mass vaccination was halted in 1979 only to resume in 1996) and, unlike countries with consistently high vaccine coverage, they have not witnessed a drastic increase in incidence in teenagers.

Estimates for the efficacy of pertussis vaccines vary widely, though most suggest that a three-component acellular vaccine, as is used in Norway, has a primary efficacy of 75–90% [10]. Additionally, clinical and epidemiological studies support the idea that immunity to pertussis wanes rapidly enough to significantly affect the disease dynamics and age-specific incidence [11–13]. Long-term vaccine trials have been undertaken and, while they are not all in agreement (see for example [14,15]), they overall suggest that immunity induced by the three-component acellular vaccine is similar to the whole cell vaccine in both primary efficacy and duration, and estimate the duration of acellular vaccine-induced protection between five and six years (reviewed in [16]). However, to date there have been few, if any, studies that estimate the shape of the distribution of loss of immunity, which is important in predicting the efficacy of a proposed vaccination strategy. Additionally, the estimates thus far do not separate out primary vaccine efficacy from waning, nor do they account for effects of circulating levels of pertussis on both the rate at which infections occur after immunity has waned and the frequency with which immunity may be subclinically boosted by natural exposure to infection [16,5].

Using data from Norway between 1996 and 2010 we provide evidence that there is a strong indirect (herd) effect of vaccination, but that effect is mostly felt by the vaccinated cohort and not horizontally across the population as a whole. Based on the proportion of cases seen in vaccinated and unvaccinated individuals, we show that immunity has indeed waned with time, and that waning has become more apparent in recent years. Lastly, using detailed age-incidence and vaccine histories, coupled with age-specific contact patterns, we propose a method to estimate the distribution of duration of vaccine-induced immunity taking age-specific contact rates into account. The results for the mean duration (6–10 years) agree with previous work, however the considerable variance suggests that some people lose immunity very rapidly.

Table 1
Timeline of events relating to pertussis control in Norway.

Year	Event
1952	Norway begins vaccinating against pertussis with a nationally produced whole-cell pertussis vaccine (DTPw). Three doses are given within the first year of life.
1976	SYSBARN is initiated as a pilot vaccine registry in a few counties.
1983	A DTPw vaccine produced by Wellcome Evans replaces the nationally produced one.
1995	SYSVAK is introduced as a national vaccine registry.
1998	The whole cell vaccine is replaced with a three component acellular vaccine, Infanrix, produced by Glaxo-Smith-Kline.
2000	PCR is introduced as a method for pertussis diagnosis.
2002	PCR becomes a common method of diagnosis.
2006	A childhood booster dose, given at age 7-years, is added. It is a 2-component pertussis vaccine called Tetravac, produced by Sanofi Pasteur.

A timeline of pertussis control and surveillance in Norway.

2. Materials and methods

2.1. The data

The data on vaccine histories and pertussis cases came from two databases maintained by The Norwegian Institute of Public Health (Folkehelseinstituttet), called SYSVAK and MSIS. SYSVAK is a national vaccine registry that records the dates of vaccination and personal identity numbers for all individuals immunized in Norway since 1996. It also includes the data collected as part of SYSBARN, which was initiated in 1976 as a pilot project to register children who were vaccinated in the Norwegian immunization program. It eventually included 40% of the nation's population, residing in Østfold, Oslo, Hedmark, Oppland and Hordaland counties. In 1995 these data were transferred to SYSVAK, which became fully operational in 1996.

The other database, MSIS, contains records of reported pertussis incidence. MSIS is the Norwegian Surveillance System for Communicable Diseases containing information on all notifiable diseases (except influenza) based on data from microbiological laboratories and doctors in Norway. The data contain personal identity number, month and year of diagnosis, county of residence and place of infection. MSIS and SYSVAK were linked for the purpose of this study so as to provide complete information on an individual's vaccination and infection histories. Identifying information about the individuals in question was stripped for privacy reasons. Incidence was calculated using yearly data on Norwegian population size from Norhealth [17], which is a national, interactive database presenting key statistics on health, disease prevalence and risk factors based on data collected from several national health registers and surveys. See Table 1 for a summary of changes in pertussis vaccination and reporting in Norway.

Mossong et. al. [18] kindly provided their original data on age-specific contact rates in European countries (herein referred to as the POLYMOD data). Norway itself was not a part of their study, so combined data from all of Europe was used, as in [3]. Also following Rohani et al., we assume that transmission is symmetric, that is, there is the same transmission rate from age group i to age group j as from j to i. Additionally, we assume that the contact patterns change smoothly with age. We therefore symmetrized and

smoothed the contact matrix using a smoothing spline with 20 degrees of freedom.

Surveillance data from the period March 1996 to October 2010 were used, with a total of 49,052 primary infections. When year-long cohorts were needed, only the data from January 1997 to December 2009 were used. Each year, between approximately 80,000 and 90,000 pertussis tests were performed, leading to about a 5% probability of a test returning positive. This probability was somewhat lower for cases tested by PCR (2–5% positive rate), which became a common diagnostic method in 2002 as cultured nasopharyngeal swabs decreased in frequency. Serological diagnosis was used frequently throughout the entire time period and approximately 65–70% of the reported cases were diagnosed by serology. Some of these tests were in young children who had recently been vaccinated, thereby potentially leading to false positive diagnoses. Additionally, serological lab diagnostic thresholds were not standardized among counties, nor were they consistent through time. Because of this, where possible, we showed that the broad results hold for the 4632 cases that were confirmed by PCR or culture.

2.2. Time series analysis

Periodicity was quantified by estimating the spectral density of the time series of reported pertussis cases. A randomization test was performed using 10,000 permutations of the data to identify significant periodicity in the data. A time-varying analysis of the periodicity for different age groups (0–0.5, 0.5–1, 1–4, 5–9, 10–20, 20–34, 35–50, and 50–80 years) was computed via wavelet decomposition of the time series for each of these age groups [19,20]. The signature of annual cyclicity was compared among these age classes by computing the difference in weeks between the annual peak between the 0–6 month old reference group and each other age group, following [21].

2.3. Survival analysis

Hazards in 0–6 month olds were calculated as the number of cases that occurred in annual cohorts before the age of six months divided by the total number of births in each year. This provides an estimate of the probability of becoming infected within the first six months of life.

We calculated the yearly attack rate for individuals having received exactly three doses of vaccine. We found the cumulative number of cases for each cohort, the cases per year, the number of never-infected, susceptible individuals and the attack rate, (equal to cases/susceptibles). The denominator for each year, which represents the pool of susceptibles, is determined by the size of the cohort minus all the cases that have occurred up to that year. This assumes perfect reporting, which is undoubtedly not true since reporting rates are estimated to be only around 10% and vary with age [22]. Incorporating the under-reporting would reduce the denominator, and increasingly so as cohorts age, thereby increasing the attack rate. Therefore, the results presented represent minimum estimates of the attack rates and are for the most part comparable between, but not necessarily within, cohorts.

Since we only have case data starting in 1996, we do not know the denominators for cohorts who received their third vaccination before 1996. To deal with this, we assume that the number of cases that occurred before observation began in 1996 was equal to the mean number of cases based on later cohorts from which we have data. This is likely to be a conservative estimate since the overall number of cases has been increasing through time. We estimated smoothed hazards as a function of time since vaccination with a binomial regression on a polynomial b-spline matrix (df = 4) using a complementary log-log link [23,24].

2.4. Loss of vaccine-induced immunity

If all of the cases in vaccinated hosts were due to primary vaccine failure, the predicted ratio of cases in vaccinated versus unvaccinated individuals should be

$$\text{proportionofcasesinvaccinatedhosts} = \frac{v(1-e)}{(1-v)+v(1-e)} \quad (1)$$

where v is vaccine coverage and e is primary vaccine efficacy. Furthermore, if immunity is not lost, this proportion of cases will be constant across age. In contrast, if infections in vaccinated individuals are due to immunity waning, the proportion in vaccinated hosts should increase with time since vaccination.

2.5. Loss of immunity model

We assume that there are two processes that determine the duration from vaccination to subsequent infection: (1) immunity wanes at some rate and (2) reinfection occurs at some presumably age-dependent rate. Using detailed data on age-specific contact patterns in Europe from the so-called POLYMOD study [18], which have shown to be applicable to pertussis [3], we can separate out these two processes and thereby estimate the kernel of waning immunity.

The following assumptions are made: (1) changes in the age distribution over time are negligible. (2) Long-term trends in the force of infection, for example due to evolution of increased virulence or changes in vaccine type, are negligible. (3) The epidemic dynamics are negligible and the number of infections is constant through time. (4) Immunity is a binary process: a host may either be completely immune to any result of pathogen exposure (infection, disease, or immune boosting) or susceptible to all. (5) The POLYMOD data on interactions between age groups accurately capture the relevant age-specific contact rates.

We fit the model to the subset of the data for which people became infected for the first time after receiving exactly 3 doses of vaccine, the third dose of vaccine was received between 9 and 15 months of age, and infection occurred before the age of 16 years. There were many cases in older adults, but because SYSVAK was introduced in 1996, these cases did not have systematic vaccine history information.

We did not include secondary or later infections because these are associated with complex ascertainment biases due to differential disease severity upon re-infection. For the age-specific mixing, we assumed that people received their third dose exactly at age 1 year and average the age-specific contact data for all of Europe. To calculate the age-specific forces of infection, we used all cases identified in Norway between 1996 and 2010. We assume that the force of infection on people of age a is proportional to the proportion of infections in each age class weighted by the age-specific contact rate. We take the weights from data provided by Mossong et al. This can be formalized as follows.

Let λ_a be the force of infection acting on age class a, $\beta_{a,i}$ the contact rate between age classes a and i, and I_i the number of infections in age class i according to:

$$\lambda_a \propto \lambda\prime_a = \sum_i \beta_{a,i} I_i \quad (2)$$

$\lambda\prime_a$ can be scaled to have a mean of one, so λ_a reflect an average force of infection, $\bar{\lambda}$.

$$\lambda_a = \bar{\lambda} \frac{\lambda\prime_a N}{\sum_a \lambda\prime_a} \quad (3)$$

where N is the number of age classes. The age-specific force of infection, λ_a, is therefore the rate (per year) at which susceptible

individuals of age a become infected. The probability that an individual who is susceptible at the beginning of age a becomes infected during the following year is then $1 - e^{-\lambda a}$.

We compare two different models of the waning of immunity kernel, (1) a gamma distribution and (2) a non-parametric distribution, defined as:

1. $W \sim \text{Gamma}(\sigma_G, \mu_G)$ and $P(I = t) = 1 - e^{\lambda t}$ where μ_G is the rate and σ_G the shape parameter, and
2. W is a discrete distribution, with 16 probabilities, one for each year-long age class between one and 16 years and one for over age 16.

To observe an infection at age t after efficacious vaccination at age 1, it is therefore necessary for immunity to have waned after τ years (where $\tau < t$), no infection to occur between ages τ and t, and then infection to occur at age t.

$$P(obs = t|\text{efficaciousvaccine}) = \sum_{\tau} P(W = \tau) * (1 - P(\tau < I < t)) * P(I = t) \quad (4)$$

Finally, we include the parameter ν, representing primary vaccine efficacy, which denotes the proportion of vaccinations which provide at least short term protective immunity. We also estimate this parameter. The final equation for probability of observing an infection at time t then becomes:

$$P(obs = t) = \nu P(obs = t|\text{efficaciousvaccine}) + (1 - \nu) * (1 - P(I < t)) * P(I = t) \quad (5)$$

Eqs. (2)–(5) provide the predicted age-distribution of cases given the following parameters: waning of immunity distribution parameters (σ and μ, or all 16 Ws), primary vaccine efficacy (ν) and the average force of infection ($\bar{\lambda}$). These equations therefore provide the basis for our likelihood estimation. We assume that the age distribution of cases is a random draw from a multinomial distribution. We calculate the likelihood of the data, that is, the number of cases in each year-long age class, given the model-predicted probability of infection at each age (Eqs. (2)–(5)). To minimize the negative log-likelihood function and find the maximum likelihood estimates for the parameters described above we used simulated annealing to identify the region in which a global optimum lies followed by an implementation of the Nelder–Mead algorithm to find the local optimum. Both of these algorithms are standard options in the function `optim` in program R [23]. We compute 95% confidence intervals for the parametric estimates by inverting the Hessian according to standard likelihood theory [24].

3. Results

3.1. Pertussis epidemiology in Norway

As in much of the highly vaccinated world, incidence of whooping cough has increased over the past 15 years (Fig. 1a). Although multi-annual cyclicity is not highly pronounced in Norway (Fig. 1b), there is statistical evidence for two to three year cycles (Supplemental figure 1). Concurrent with the increase in total cases, there has been a shift in the age structure, with a greater proportion of cases in teenagers and adults now, and a smaller proportion in infants and young children (Fig. 2). Incidence in children under the age of five years has not changed much over the fifteen-year time period, however incidence in teenagers and young adults (10–40 years) has increased dramatically (Fig. 3a). Children between the ages of five and ten years experienced an increase in incidence from 1997 until the introduction of the childhood booster

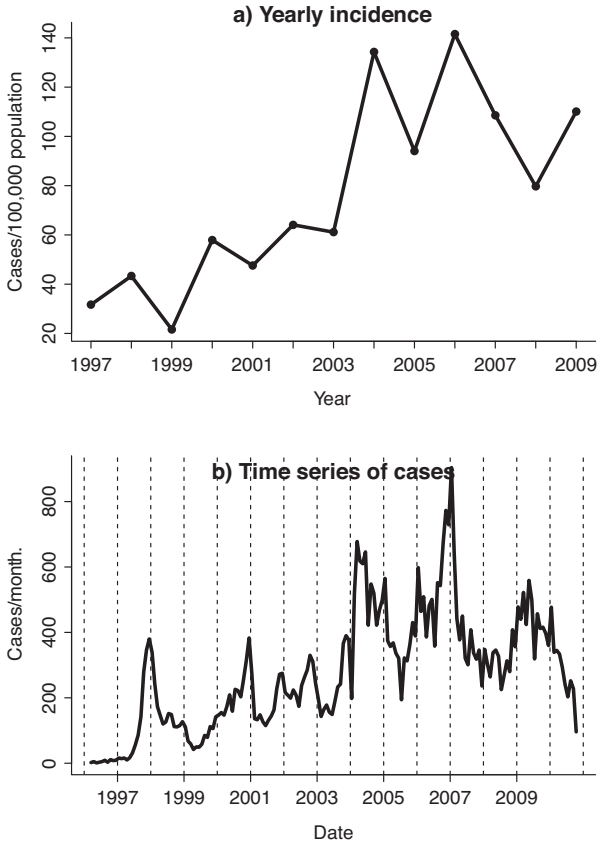

Fig. 1. Temporal increase: (a) annual incidence per 100,000 population and (b) monthly case reports show an overall increasing trend across the 15-year period of this study. (a) Shows incidence during the time period during which we have data from entire years, therefore we do not include 1996 and 2010. All cases reported to MSIS are included in (b). The dotted vertical lines indicate January 1st of each year.

vaccine in 2006, and have now returned approximately to their 1997 levels. In contrast, there was a milder downturn in incidence in 10–19 year olds in 2006, followed by an increase a few years later.

The data show an annual peak in November, however the seasonality varies among age groups with pre-school age children (0–5 years) exhibiting a summer peak, school-age children (5–20 years) a winter peak, and adults (20–80 years) beginning to increase in the summer and remaining high through the winter (Fig. 3b). Outbreaks in infants (0–6 months) occur simultaneously with those in children under the age of five and adults, but approximately 12 weeks prior to those in school-age children (Supplemental figure 2). Together, these analyses suggest that infant pertussis in Norway is not frequently caused by cases in teenagers, but may be caused largely by younger siblings and parents.

3.2. Age effects and indirect protection

Vaccinated children who are too young to receive the booster vaccine (under the age of seven) are infected more quickly at the end of the fifteen-year study period than at the beginning (Fig. 4). The downward trend appears to begin in 1998, the year in which the acellular vaccine was introduced. The qualitative results are the same whether looking at the full data set (Fig. 4a) or the subset of cases diagnosed by PCR or culture (Fig. 4b). We scrutinize this trend further using survival analysis to estimate the risk of infection for various cohorts. These hazard regressions show that the risk of becoming infected after three-doses of vaccine has increased dramatically for cohorts of teenagers, but has not changed significantly

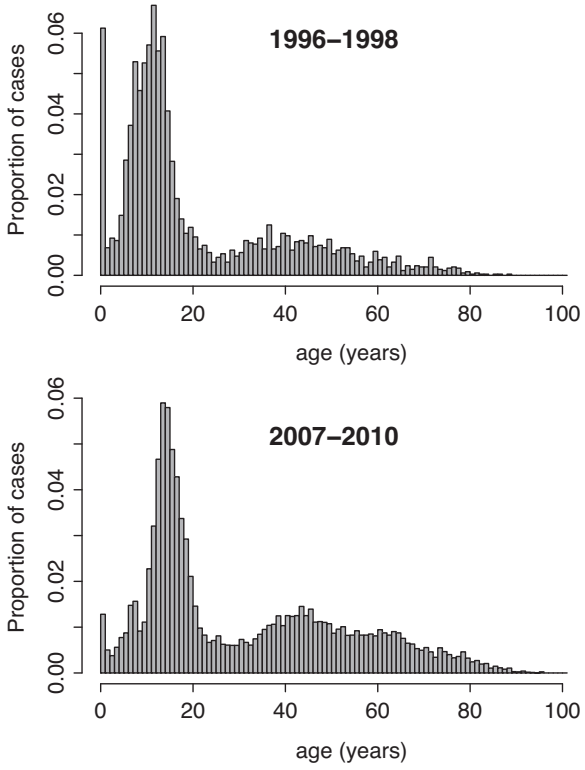

Fig. 2. Age distribution shift. Proportion of cases in each year-long age class, from diagnoses between (a) March 1996 and December 1998, and (b) January 2007 and October 2010.

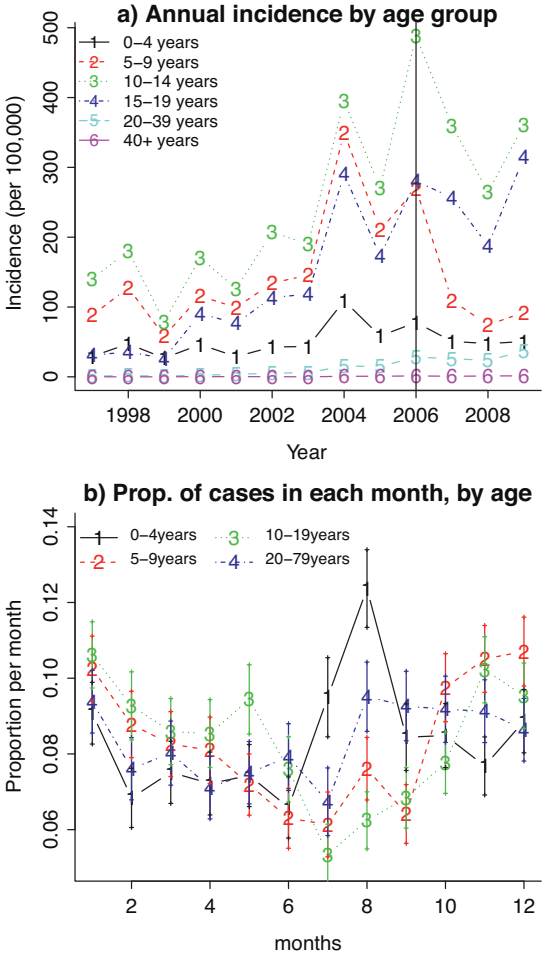

Fig. 3. Age incidence and seasonality: (a) annual incidence per 100,000 people in each age group from 1997 to 2009. The black vertical line at 2006 indicates the introduction of the childhood booster dose at age 7. (b) The proportion of cases in specific age groups that occurred in each calendar month. Vertical lines show 95% confidence intervals assuming binomially distributed data.

for 0–6 month old infants in whom pertussis infection can cause severe disease (Fig. 5a). The introduction of the booster in 2006 did not have a large impact on either of these groups, though it may have contributed to the slight decrease in risk for infants.

The national vaccine registry uniquely allows us to investigate the risk that is experienced by children who received only the first three doses of vaccine but were part of a cohort in which many of their peers received a booster dose six years after the third dose (i.e. the within-cohort herd immunity). The cohort of individuals who received the third dose in 1999 was the first to attain high coverage with the booster. In that cohort and all that followed, the children who did not receive the booster vaccine experienced a marked decrease in risk of infection, indicating strong indirect protection within the cohort (Fig. 5b). However, the between-cohort effect was not strong, as the 1996 and 1997 cohorts exhibited increased risk into the teen years, though their increase was not as smooth and monotonic as the cohorts preceding them (Supplemental figure 3), which could be indicative of a milder level of indirect protection provided by the booster to these neighboring cohorts. Additionally, the data hint that the indirect effects of the vaccine may be beginning to wear off by around eleven years post 3rd vaccination (five years after the cohort was boosted), as there is a slight upturn in the risk at this point (Fig. 5b).

3.3. Loss of vaccine-induced immunity

The above results are consistent with and suggestive of significant loss of immunity. However, the high incidence in the teenage years could be due to a combination of primary vaccine failure, estimated to be between ten and twenty-four percent for three-component acellular pertussis vaccines [10], and high teen–teen contact rates rather than increased susceptibility due to immune waning. In order to distinguish between these two possibilities, we consider the proportion of all cases that occur in vaccinated hosts.

The data clearly reflect the prediction from immune waning, with the proportion increasing from the very beginning up to approximately age 15 (Fig. 6). By age 14 over 90% of cases occurred in vaccinated hosts, which, in the absence of loss of immunity, would indicate vaccine efficacy below 30% (Eq. (1) and Supplemental figure 4). These results therefore provide strong evidence that vaccine-induced immunity wanes over time.

3.4. Modeling loss of immunity

In order to inform vaccine policy, it would be useful to have an estimate of the full statistical distribution of how long immunity lasts after vaccination (the waning kernel) with which we could model the impact of different vaccination strategies. The age distribution of cases holds information on the waning process, and we therefore compare predicted age distributions with the observed one using a multinomial likelihood.

The mean duration of immunity estimated from the full data set is in the range of 6–10 years (Table 2). There appear to be substantial heterogeneities however (as was suggested by the analysis of proportion of cases in vaccinated hosts) and immunity appears to wear off in some hosts quite quickly. The waning kernels estimated from the full data set suggest that between 15 and 30% of hosts lose immunity within the first five years after vaccination.

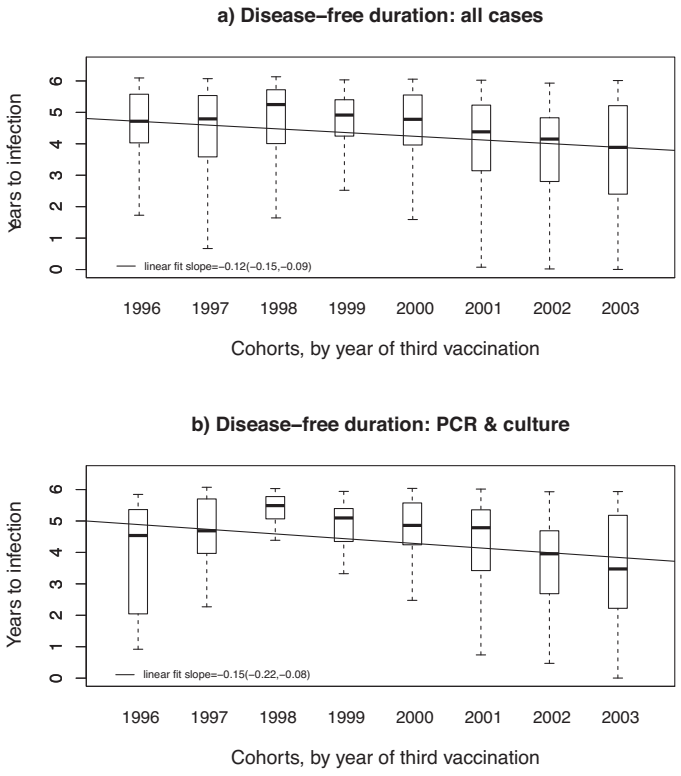

Fig. 4. Disease-free durations by cohort. Boxplots represent the 1.5 × inter-quartile range (whiskers) and quartiles (horizontal lines), and best-fit lines show the mean trend of the duration between third dose of vaccine and subsequent infection in children too young to receive the booster vaccine. (a) Includes all cases identified in individuals who (i) received his/her third dose of vaccine between the ages of 9 and 15 months, (ii) received the third dose between January 1, 1996 and December 31, 2003, and (iii) was younger than 7 years of age when infected. These criteria control for differences in age-specific contact rates, right-censoring, and effects of the childhood booster, respectively. (b) Includes a subset of the above cases, with the additional criterion that the infection was confirmed by either PCR or culture, thereby avoiding false positive serological diagnoses.

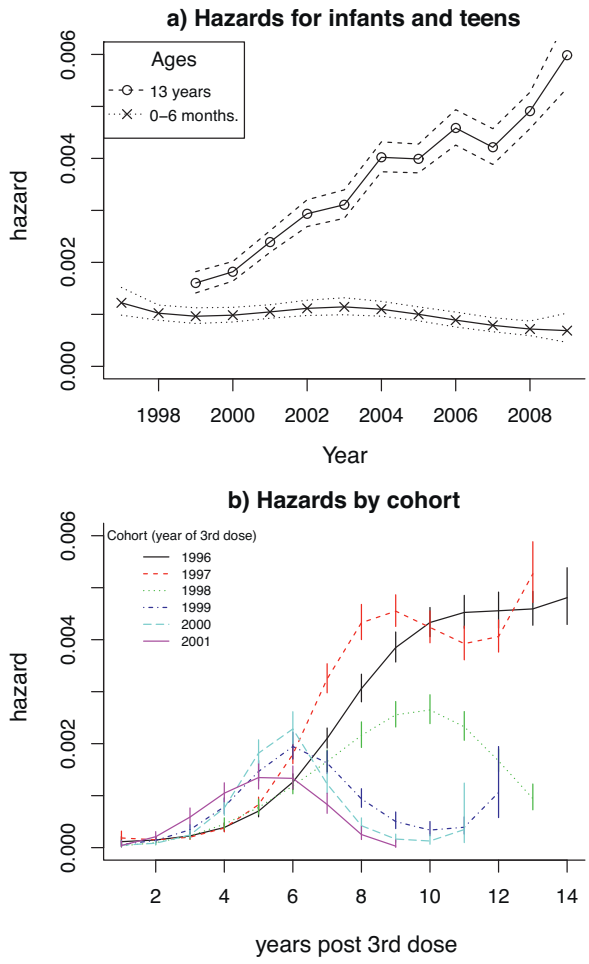

Fig. 5. Hazards over time: (a) hazard of infection in the first six months of life (×) for annual cohorts of infants born between January 1, 1997 and June 1, 2009. Hazard of infection from 1999 to 2009 for 13 year-olds (circles) who received their third dose of vaccine between January 1, 1987 and December 31, 1997. Dotted and dashed lines represent 95% confidence intervals. (b) Hazards for annual cohorts, defined by the year in which individuals received their third dose of vaccine. The 1999 cohort was the first to receive substantial coverage with the childhood booster dose, introduced in 2006. Vertical lines represent 95% confidence intervals.

The results are sensitive to which subset of the data we use. When only considering the age distribution of cases that occurred between 1996 and 1999, the mean duration of immunity is estimated to be as low as three to four years, while the later subset (2007–2010) suggests over ten years of protection on average. We also estimated the distribution non-parametrically and found that the distribution is bimodal, with a peak in the 5–6-year range, and another in the 10–12-year range (Supplemental figure 5). This model has by far the best fit, even accounting for the large number of parameters (AIC = 172, Table 2).

4. Discussion

The epidemiology of pertussis in Norway has been changing over the past 15 years in that there is (1) increasing incidence, (2) a shift in age distribution toward cases in teenagers, and (3) a decrease in the long-term protection provided by the vaccine.

Table 2
Parameter estimates.

Data set	Model	Mean (years)	sd (years)	Efficacy	Hazard	AIC
Total	Gamma (fixed)	9.4 (8.9, 9.8)	4.40 (4.39, 4.42)	0.82 (fixed)	0.02 (fixed)	262
	Gamma	6.5 (6.1, 6.8)	2.7 (2.5, 2.9)	0.73 (0.71, 0.76)	2.2E-9 (2.1E-9, 2.4E-9)	228
	Nonparametric	9.6	10.1	0.82	0.02	172
1996–1999	Gamma (fixed)	3.6 (3.2, 4.1)	1.5 (1.1, 1.9)	0.82 (fixed)	0.02 (fixed)	322
	Gamma	6.3 (5.7, 6.9)	2.5 (2.4, 2.6)	0.86 (0.81, 0.9)	0.076 (0.065, 0.09)	234
2007–2010	Gamma (fixed)	10.3 (10.1, 10.5)	1.4 (1.3, 1.5)	0.82 (fixed)	0.02 (fixed)	342
	Gamma	12 (11.8, 12.1)	2.22 (2.16, 2.29)	0.96 (0.95, 0.97)	0.22 (0.20, 0.23)	206

Maximum likelihood estimates are shown for model fits to the age distribution from (1) all the data combined, (2) just the early years (1996–1999), and (3) just the recent years (2007–2010). Using the full data set, the model was fit in three different ways: (1) assuming gamma distributed loss of immunity with fixed primary vaccine efficacy and mean hazard (force of infection), (2) assuming gamma-distributed loss of immunity and estimating primary vaccine efficacy and the mean hazard, and (3) non-parametrically. For the other two data sets, only the first two estimates were performed. Values in parentheses indicate 95% confidence intervals. The non-parametric distribution is shown in Supplemental figure 5.

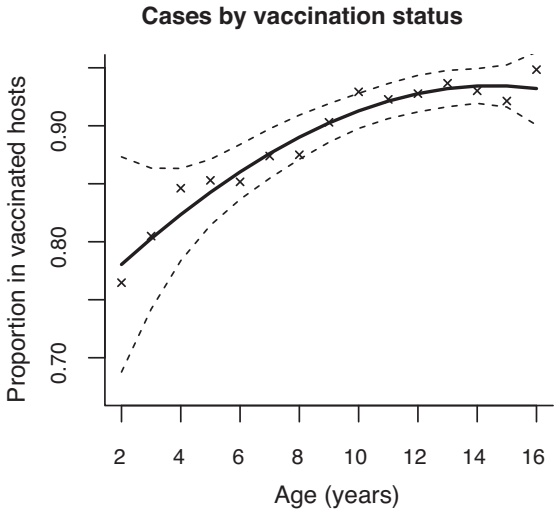

Fig. 6. Proportion of cases in vaccinated hosts. Proportion of cases in vaccinated hosts, using data from counties that were part of SYSBARN. The proportions in each year-long age group are denoted by ×. The solid black line shows the smoothed trend (b-spline basis with 3 df), and the dashed lines the 95% confidence interval.

These results parallel those seen in Massachusetts, another population with both high vaccine coverage and surveillance, during a similar time period [13]. The carefully documented "natural experiment" that took place with the addition of a booster vaccine at age seven shows strong indirect or herd protection, caused by reduced transmission, within age groups, but not very much between age groups. This observation is in line with other work that shows strong teen–teen transmission and with social network studies [18] that reveal a highly diagonal who-acquires-infection-from-whom (WAIFW) matrix, indicating strong mixing within age groups and between parents and their offspring, but weak contact patterns elsewhere. These results are in contrast to the classic modeling assumptions of homogeneous mixing and impact the predicted utility of booster vaccination campaigns.

There is strong evidence that immunity wanes with time, and that cases in teenagers are not solely caused by primary vaccine failure and age-specific contact rates. Additionally, the process of waning begins soon after vaccination in a substantial proportion of people. However, quantifying the distribution of time it takes for immunity to be lost is difficult. We presented a method for estimating the distribution of loss of immunity that takes into account the time it takes between loss of immunity and infection in an age specific manner. Although the results are for the most part in agreement with previous estimates, they are sensitive to the subset of the data and are therefore not a satisfactory final answer. The most preferred model suggests a bimodal distribution of durations of immunity. This may be indicative of sub-populations of hosts or pathogens that respond differently to the vaccine. However, it is also possible that the bimodality and inconsistencies between estimates indicate that the violation of the model assumptions is not negligible when estimating the duration of immunity. In particular, as we have shown, the age distribution of cases changed significantly through time, and there is evidence to suggest that the force of infection may also have been increasing throughout this period. Additionally, studies suggest immunity to pertussis is not simply present or absent, but rather the degree of protection against symptomatic disease decreases gradually as immunity wanes [25].

A dynamic approach that accounts for temporal trends in incidence and pathogen virulence, cyclic dynamics, and assumes a more realistic model of immunity may help to provide robust estimates of the duration of vaccine-induced immunity. This can potentially be achieved through a combination of previous approaches, such as assuming a model of immunity similar to that in [5] combined with a stochastic, dynamic estimation procedure such as that used in [3]. Unfortunately, we were not able to assess whether the duration of immunity induced by the acellular and whole-cell vaccines was different because the effects of the change in vaccine type was confounded by the introduction of the childhood booster. The first birth cohort to get the childhood booster at age 7 was born in 1999 and therefore there was only one transitional cohort who received 3 doses of acellular vaccine and no booster.

In the face of our discoveries, an obvious question is: what would be the impact of introducing a teenage booster vaccine to Norway? The experience with the introduction of the booster at age seven suggests we might see significantly reduced transmission and disease in teenagers, which would be useful by itself. However this may not have a large impact on cases in infants since there is little transmission between these age groups and herd immunity appears to be surprisingly within-cohort restricted. If immunity wanes as rapidly after a teenage booster as it does after the primary three doses, we would expect little protection of the parenting-age population, who have frequently been identified as a main source of severe pertussis to infants [9]. Finally, it is conceivable that by vaccinating teenagers we would further erode the immunity that exists in adults of child-bearing age and thus increase circulation in this age group. To fully assess the likelihood of these possible outcomes, a better understanding of the causes of the changes in pertussis epidemiology over the past 15 years is necessary. We do not yet understand the combined effects of complex immune kinetics and changes in pathogen populations in this dynamic system. At this point, the predictions we can make regarding the utility of a teenage booster vaccine are that (1) it will reduce incidence in teenagers and (2) it is unlikely to have a large effect on infant pertussis.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.11.065.

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